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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,119	01/12/2005	W. Wayne Lautt	14430.6USWO	3382

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EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,119	LAUTT ET AL.	
	Examiner	Art Unit	
	SAHAR JAVANMARD	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-40 and 47-64* is/are pending in the application.

4a) Of the above claim(s) *9-21, 23-47, 49, 51, 53, 55, 57, 59, 61, and 63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,48,50,52,54,56,58,60,62 and 64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/13/07; 05/06/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

This Office Action is in response to Applicant's Restriction Requirement remarks filed on January 31, 2008. Claim(s) 19-40 and 47-64 are pending. Claim(s) 19-21, 23-47, 49, 51, 53, 55, 57, 59, 61, and 63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant's election of Group III drawn to a method of increasing glucose uptake by skeletal muscle of a patient, comprising administering a phosphodiesterase antagonist and election of species of antagonist tadalafil without traverse of the restriction requirement in the reply is acknowledged.

The phosphodiesterase antagonist tadalafil was found free of the art and the search for other antagonists was expanded.

The requirement is deemed proper and is therefore made FINAL. Claim(s) 22, 48, 50, 52, 54, 56, 58, 60, 62, and 64 are examined herein insofar as they read on the elected invention and species.

Claims Warning

Applicant is advised that should claim 54 be found allowable, claim 56 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing

one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Objections

Claims drawn to non-elected inventions have incorrect claim status identifiers (i.e., 19-21, 23-47, 49, 51, 53, 55, 57, 59, 61, and 63). Appropriate action is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22, 50, 52, 54, 56, 58, 60, 62, and 64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for some phosphodiesterase inhibitors, namely, at least one of vinpocetine, zaprinast and dipyridamole, sildenafil, theophylline, aminophylline, isobutylmethyl xanthine anagrelide, tadalafil, dyphylline, vardenafil, cilostazol, caffeine, milrinone, amrinone pimobendan, cilostamide, enoximone, teroximone, vesmarinone, rolipram or R020-1724, does not reasonably provide enablement for a method of increasing glucose uptake by skeletal muscle comprising administration of any phosphodiesterase antagonist as set forth in the instant claims. The specification does not provide sufficient information that all phosphodiesterase antagonists are capable of increasing glucose uptake by skeletal

muscle. Thus, the term phosphodiesterase antagonist is very broad as cited in claims 22, 50, 52, 54, 56, 58, 60, 62, and 64.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The specification does not provide sufficient information that all phosphodiesterase antagonists are capable of increasing glucose uptake by skeletal muscle.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

All of the rejected claims are drawn to an invention which pertains to a method of increasing glucose uptake by skeletal muscle with the administration of a phosphodiesterase antagonist claims 22, 50, 52, 54, 56, 58, 60, 62, and 64.

The nature of the invention is complex in that it encompasses the treatment of said ailments using a wide array of compounds encompassed by the term phosphodiesterase antagonist.

(2). Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass methods of promoting increasing glucose uptake by skeletal muscle by administering by a wide array of compounds encompassed the term phosphodiesterase antagonist. There are countless possible compounds encompassed by phosphodiesterase antagonist for the treatment claimed. The claims are therefore much broader than the enabling disclosure.

(3). Guidance of the Specification:

The specification states that any suitable phosphodiesterase antagonist may be employed. The specification further states that a phosphodiesterase antagonist will be "suitable" if: (a) at the dose and method of administration to the mammalian patient, it is not acutely toxic, and does not result in chronic toxicity disproportionate to the therapeutic benefit derived from treatment; and (b) at the dose and method of administration to the mammalian patient it reduces insulin resistance in the patient (page 8, lines 22-27). Although this is stated, there is no further guidance on actual data other than the working example as described below.

(4). Working Examples:

Applicant provides and example of methods for reversal of HISS-dependent insulin resistance using a phosphodiesterase inhibitor, namely zaprinast, in normal rats.

(5). State of the Prior Art:

The state of the prior art regarding phosphodiesterase inhibitors is high.

(6). Nature and predictability of the invention

The nature of the invention is directed towards medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(7). The Quantity of Experimentation Necessary:

In order to practice the claimed invention, one of skill in the art would have to first envision a combination of an appropriate pharmaceutical carrier, a dosage for each compound as encompassed by phosphodiesterase antagonist, the duration of treatment, route of treatment, etc. and, in the case of human treatment, an appropriate animal model system for one of the claimed compounds. One would then need to test the combination in the model system to determine whether or not the combination is effective for increasing glucose uptake by skeletal muscle. If unsuccessful, which is

likely given the lack of significant guidance from the specification or prior art regarding increasing glucose uptake by skeletal muscle treatment with phosphodiesterase antagonist, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above and test the system again. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to increasing glucose uptake by skeletal muscle by administration of one of the phosphodiesterase antagonists as set forth in the claims.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, methods of increasing glucose uptake by skeletal muscle thereof by administering the various phosphodiesterase antagonists of the claims is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said

subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22, 50, 52, 54, 56, 58, 60, 62, and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamasaki et al. (EP 1020452 A1) in view of Lautt (Can. J. Physiol. Pharmacol., 1999).

Yamasaki teaches benzimidazole derivatives and their pharmaceutically acceptable salts as having blood sugar level-depressing activity or PDE5-inhibiting activity (page 3, lines 5-8). Yamasaki teaches that these compounds are useful for preventing and treating impaired glucose tolerance, diabetes related disorders, insulin resistance and many other ailments (page 3, lines 11-29).

Yamasaki further teaches that these derivatives along with pharmaceutically acceptable carriers are suitable for oral administration, parenteral administration, or

external application (page 13, lines 4-9). For oral administration, the dose of the derivative may be from 1 to 100 mg/kg and for intramuscular or intravenous injection, it may be from 0.1 to 10 mg/kg.

Yamasaki does not teach the uptake of glucose as it specifically pertains to skeletal muscle.

Lautt teaches glucose uptake in response to insulin is largely dependent upon uptake in skeletal muscle (abstract; page 557, "Skeletal muscle as the resistant tissue").

It would have been obvious to one of ordinary skill in the art to have known that the increase in glucose uptake upon administration of a phosphodiesterase inhibitor as taught by Yamasaki would be done so in large part by skeletal muscle, as taught by Lautt.

Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yamasaki et al. (EP 1020452 A1) in view of Lautt (Can. J. Physiol. Pharmacol., 1999) as applied to claims 22, 50, 52, 54, 56, 58, 60, 62, and 64 above in further view of Nakaya (Diabetes, Obesity, and Metabolism, 1999).

Yamasaki and Lautt are discussed above.

Neither Yamasaki nor Lautt teach any of the phosphodiesterase antagonists as recited in claim 23 (i.e., vinpocetine, zaprinast and dipyridamole, sildenafil, theophylline, aminophylline, isobutylmethyl xanthine anagrelide, tadalafil, dyphylline, vardenafil,

cilostazol, caffeine, milrinone, amrinone pimobendan, cilostamide, enoximone, teroximone, vesmarinone, rolipram and or R020-1724).

Nakaya teaches cilostazol, a phosphodiesterase III inhibitor, has a beneficial effect on insulin sensitivity in patients with non-insulin dependent diabetes mellitus (NIDDM) (page 40, column 2, 3rd paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed the phosphodiesterase inhibitors used to treat impaired glucose tolerance, diabetes related disorders, and insulin resistance as taught by Yamasaki and also used cilostazol as the phosphosdiesterase inhibitor. The motivation provided by Nakaya demonstrates that cilostazol also improves insulin sensitivity. Thus one would expect with a reasonable degree success that cilostazol could be employed in order to increase glucose uptake by skeletal muscle.

Conclusion

Claims 22, 48, 50, 52, 54, 56, 58, 60, 62, and 64 are not allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sahar Javanmard whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

SJ

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617